## DETAILED ACTION

### *Specification*

The amendments to the specification submitted 23 June 2009 are noted and the comments are withdrawn.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14, 16, 17, 20, 22, 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deisher et al. (WO 98/51333), Skinner et al. (US 2003/0228371 A1) and Dardik et al. ((2003) Arterioscler. Thromb. Vasc. Biol. 23: 1472-77). Deisher et al. teach methods and compositions useful in treatment of reducing ischemic reperfusion injury and reducing necrotic tissue damage and/or vascular injury resulting from ischemic reperfusion by administration of compositions of factor XIII. See Example 1, and page 1, lines 9-16 (instant claims 9, 11, 14, 16, and claims 19-24 in reference to diseases to be treated that are characterized by the presence of ischemic tissue, i.e. obstruction of the blood flow).

Deisher et al. teach methods for reducing ischemic reperfusion injury, reduction in tissue damage, vascular injury, myocardial infraction or stroke in a patient, wherein an effective amount of factor XIII is administered to a patient; and where the ischemic reperfusion injury addresses all diseases which are associated with disturbed blood perfusion and thus include instant claims that refer to stimulating the perfusion of ischemic tissues. See page 7, lines 25-28; page 9, lines 24-29; and page 11, lines 2-3; page 7, lines 10-17 (instant claims 9, 11, 14, 16, and 19-24 where all the diseases claimed suffer from disruption of a blood flow to the tissue, i.e. ischemia, for example).

Deisher et al. teach that the factor XIII compositions are administered to the patient as a bolus injection (p.7, lines 28-31 (instant claims 9, 11, 12, 14, 16, 17)). They also teach that the factor XIII compositions can be administered as gels, foams or bandages, i.e., topical administration (p.8, lines 5-7 (instant claims 10, 13, 15, 18)). They do not specifically teach administration of Factor XIIIa, however they teach administration of many variations of the Factor XIII complex, including the a2 dimer (p. 18) and recombinant Factor XIII (p. 19).

Skinner et al. teach "methods, wherein the step of assaying comprises using the mouse MCAO model of cerebral ischemia. Also disclosed are methods utilizing models of new vessel angiogenesis, remodeling, reperfusion damage, and tests for whole body ischemia" [0127]. As well, they disclose "methods, wherein the step of assaying comprises using the mouse MCAO model of cerebral or myocardial ischemia. Also disclosed are "methods wherein the step of assaying comprises using the rat model, or any other animal model, such as mammalian models, of coronary artery occlusion for myocardial or cerbral ischemia. Also disclosed are methods utilizing animal models of new vessel angiogenesis, old vessel remodeling where collateral anastomoses open wider to fill distal ends of blocked vessels, reperfusion damage where high-levels of accumulated byproducts of ischemia enter the distal ischemic tissues and/or osmosis-induced organelle or membrane damage occurs in ischemic tissues, and wherein any other organ is made ischemic or wherein all the organs and tissues are made ischemic by whole-body ischemia induced by temporary cardiac arrest (e.g., ventricular fibrillation) or blockade of flow (e.g., clamping of aortic output). There are a variety of other models that are adjunctive to the more conventional ischemia (vessel-occlusion)/infarction (engendered-necrosis) models. For example, infarction can be engendered by trauma from a mechanical blow, coagulopathy from a snake venom, and so on. Similarly ischemia can be evoked slowly by ameroid constrictors, produced in small distal vessels by infused microspheres, and so on. Furthermore these models can be modulated by global variants such as gene-knockout (e.g., myocardial receptor deletions), bio-behavioral modifications (e.g., psycho-social stress), and so on" [0082].

They do not teach the specific administration of Factor XIIIa, however they teach the use of molecules related to Factor XIIIa, stating "FPA is a fragment of soluble fibrinogen, which is

released upon cleavage of fibrinogen by thrombin. The thrombin (IIa) catalyzed cleavage of soluble fibrinogen (Fbg) to form fibrin (Fbn) is the terminal proteolytic event in the coagulation cascade. These soluble Fbn monomers spontaneously polymerize to form an insoluble Fbn network which is stabilized by the factor XIIIa catalyzed crosslinking of lys and glu residues of a and g chains. This Fbn network is the major protein component of the haemostatic plug." And, "FPA is the N-terminus of the Aa chain, which contains factor XIIIa crosslinking sites and 2 phosphorylation sites" [0131-33].

They teach that "[i]t is understood that infarctions, which are regions of necrotic tissue can arise in a variety of ways, but typically an infarction will arise from an ischemia, or a reduction of oxygen to a region of tissue. The loss of oxygen, and the subsequent reperfusion, should it occur, can cause necrotic tissue to arise. The disclosed methods are designed to reduce the effects of ischemic events, such as infarctions caused by reperfusion and/or oxygen deprivation. These types of events occur, for example, during a stroke, where there is blood vessel blockage in cerebral tissue causing ischemia or in a cardiac event, such as a heart attack, where blockage of a coronary artery leads to ischemia." And, "[t]reatment of ischemia typically involves reduction of blockage. For example, nitroglycerin treats ischemia (opens clogged coronary vessels a little more than normal and makes angina pain from the ischemia go away). Suppression of blood flow causes ischemia. The mouse-MCAO model produces ischemia and sets the stage for infarction to occur at, typically 24-hrs. It is the infarction that is prevented/treated, as the flow has been re-established at the time of the injection the disclosed compositions and the tissue is therefore no longer ischemic. Anti-infarction molecules are

sometimes referred to as "neuro-protectant drugs." There are a variety of different types of molecules that can have FPA or bradkinin anti-infarction activity." [0195-6].

Dardik et al. teach that factor XIII participates in tissue remodeling and wound healing, and processes that involve angiogenesis, where in vivo or in vitro models were used to examine the role of factor XIII in angiogenesis, i.e, migration, proliferation of cells. See page 1447, left column, third paragraph; page 1475, left column, second paragraph; and see *Discussion* section on page 1476. This reference does not specifically teach the treatment for stimulating the perfusion of ischemic tissues.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Deisher et al. Skinner et al. and Dardik et al. to achieve the invention as claimed. As currently recited, a method of administering activated Factor XIII (Factor XIIIa) is claimed, with the result that perfusion of ischemic tissues and proliferation of new blood vessels in ischemic tissues is stimulated. As taught by the prior art, it was known that various components of the fibrinogen cascade could function to stimulate perfusion of ischemic tissues and stimulate new blood vessels. One would have a reasonable expectation of success and be motivated to use any of the known compounds that would act in this cascade in that the prior art directly addresses that multiple molecules can have anti-infarction, i.e., increased perfusion and increased blood vessel formation, activity.

***Response to Arguments***

Applicant's arguments filed 23 June 2009 have been fully considered but they are not persuasive. Applicant argues that none of the cited prior art addresses the applicability of using Factor XIII to induce blood vessel proliferation in ischemic tissues. However, Skinner et al. state

that "[t]he disclosed molecules and fractions can produce 100% reversal of infarction in some of the animals in which 1-hr occlusions are made (mouse-MCAO), including reversals in the central core, and thus the core vs. peripheral damage issue appears to be addressed. With pre-treatment by the disclosed molecule(s) and fractions after 1-hr of occlusion a tissue savings of 100% was observed at 24 hrs in all of the animals. Injection of the relevant molecule(s) show efficacy when injected out to 8-hours after the onset of the 1-hour of ischemia. A mouse requires only [fraction (1/20)]th the amount of injection material as the rat, which makes the mouse more efficient for multiple studies.

Disclosed are methods, wherein the step of assaying comprises using the mouse MCAO model of cerebral or myocardial ischemia. Also disclosed are methods wherein the step of assaying comprises using the rat model, or any other animal model, such as mammalian models, of coronary artery occlusion for myocardial or cerbral ischemia. Also disclosed are methods utilizing animal models of new vessel angiogenesis, old vessel remodeling where collateral anastomoses open wider to fill distal ends of blocked vessels, reperfusion damage where high-levels of accumulated byproducts of ischemia enter the distal ischemic tissues and/or osmosis-induced organelle or membrane damage occurs in ischemic tissues, and wherein any other organ is made ischemic or wherein all the organs and tissues are made ischemic by whole-body ischemia induced by temporary cardiac arrest (e.g., ventricular fibrillation) or blockade of flow (e.g., clamping of aortic output). There are a variety of other models that are adjunctive to the more conventional ischemia (vessel-occlusion)/infarction (engendered-necrosis) models. For example, infarction can be engendered by trauma from a mechanical blow, coagulopathy from a snake venom, and so on. Similarly ischemia can be evoked slowly by ameroid constrictors,

produced in small distal vessels by infused microspheres, and so on. Furthermore these models can be modulated by global variants such as gene-knockout (e.g., myocardial receptor deletions), bio-behavioral modifications (e.g., psycho-social stress), and so on" [0081-2].

As well, Deisher recite that "factor XIII is used...for the reduction of ischemic reperfusion injury or prevention or reduction of...[vessel] damage in a patient" (p. 7). They state that they contemplate a method of treating ischemic tissues comprising administering activated Factor XIII, which would naturally thereby stimulate the induction of new blood vessels.

## *Conclusion*

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Hobbs whose telephone number is 571-272-3373. The examiner can normally be reached on Hotelling - Generally, 9-6 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lisa J. Hobbs/
Primary Examiner
Art Unit 1657

ljh